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Influenza A virus-associated acute necrotizing encephalopathy in the United States

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During the past several years, influenza-associated acute necrotizing encephalopathy has been well-recognized in Asia but has not yet been reported in the United States. We describe a 28-month-old patient who displayed the classical clinical features of acute necrotizing encephalopathy in association with a documented influenza A infection. This disease is characterized by fever, a rapid alteration in consciousness and seizures, with radiologic involvement of the bilateral thalami and cerebellum.

INTRODUCTION

Influenza is a common infection associated with substantial morbidity and mortality in children and the elderly.[1] Neurologic complications include febrile seizures, Reye's syndrome, encephalitis, myelitis and acute necrotizing encephalopathy (ANE). During the past several years, influenza-associated ANE has been well-recognized in Asia but has not been reported in the United States. ANE is characterized by multifocal symmetric brain lesions involving the bilateral thalami, putamina, cerebral and cerebellar medulla and brainstem tegumentum.[2] The clinical course of ANE is rapidly progressive, including constitutional symptoms of cough, emesis and diarrhea in combination with neurologic dysfunction such as rapid alteration of consciousness and seizures. The disease is associated with high mortality and morbidity, with potentially severe neurologic sequelae in survivors.[3]

CASE REPORT

A previous healthy 28-month-old girl of Filipino descent presented in February to an outside hospital with persistent lethargy and confusion after a witnessed generalized tonic/clonic seizure lasting 3 min. She had a 1-day prodrome of subjective fever, rhinorrhea, cough and vomiting for which she had received a dose of oral ibuprofen and intramuscular ceftriaxone. There was no history of influenza immunization, recent travel, ill contacts or exposure to other drugs including acetylsalicylic acid.

On arrival at a local emergency room, the patient's mental status improved, and she conversed with her mother. However, during the ensuing several hours, her mental status fluctuated and then progressively declined. Rectal temperature was 42°C. She was transferred to our hospital at Day 2 of her illness because of her worsening mental status and fever.

On admission to our hospital, rectal temperature was 38°C, and other vital signs were normal. The initial laboratory evaluation included normal values of electrolytes, creatinine, bicarbonate and glucose as well as a normal urinalysis and chest radiograph. The white blood cell count was 14 800/μl with 93% neutrophils, the platelet count was 205 000/μl and aspartate aminotransferase and alanine aminotransferase were 40 and 23 IU/l, respectively. Ammonia was 11 μmol/l and lactate was 0.8 mEq/l. The cerebrospinal fluid (CSF) was clear with no nucleated or red blood cells. The CSF glucose was 89 mg/dl, and CSF protein was 26 mg/dl. An opening pressure was not obtained. Neurologic examination revealed normal reactive pupils. There were decreased muscle tone and normal reflexes in all extremities. Noxious stimulation elicited extensor posturing and bruxism. The respiratory pattern was normal and the Glasgow coma scale was 12 without significant fluctuation. Phenobarbital and lorazepam were administered intravenously for presumed seizure activity.

A computerized tomography scan showed hypodensities in the bilateral basal ganglia and thalamic regions. Magnetic resonance imaging (MRI) on Hospital Day 2 revealed lesions in the bilateral thalami, deep cerebellar nuclei, posterior midbrain and posterior periventricular white matter (Fig. 1). Magnetic resonance angiography and magnetic resonance venography were normal. Continuous electroencephalogram monitoring did not reveal any ictal activity during the

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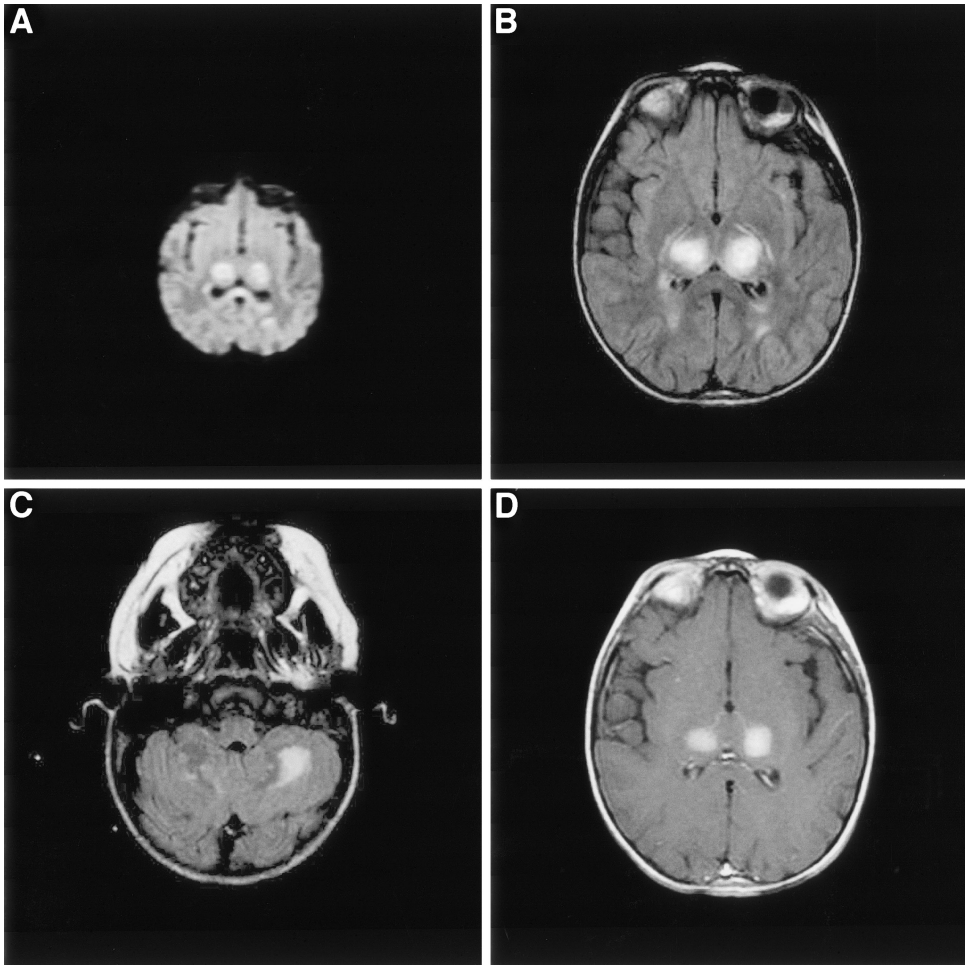

FIG. 1. Diffusion weighted imaging shows regions of restricted diffusion in the bilateral thalami and deep cerebellar nuclei bilaterally (*A*). Fluid-attenuated inversion recovery imaging of the thalamus (*B*) and cerebellum (*C*) show regions of hyperintensity corresponding to the areas of restricted diffusion. The above areas enhance with intravenous contrast (*D*).

intermittent vertical eye movements. A repeat head MRI on Hospital Day 8 demonstrated areas of increased T_1 signal in the bilateral thalami that represented small areas of hemorrhage in areas of previous infarction. Laboratory evaluation for an underlying hypercoagulable or rheumatologic condition was negative. A transthoracic echocardiogram revealed normal cardiac structure and function. Table 1 summarizes the differential diagnosis for ANE considered in this case and the workup performed.

Empiric ceftriaxone, vancomycin and acyclovir were administered for possibility of bacterial meningitis or herpes simplex virus encephalitis. Intravenous methylprednisolone at 10 mg/kg/day was initiated on Hospital Day 3 to treat for possible acute disseminated encephalomyelitis. Amantadine 2.5 mg/kg and oseltamivir 2.7 mg/kg were administered from Day 6 to 12. On Day 9, because of persistent encephalopathy, intravenous γ-globulin (IgG) at 0.2 g/kg iv was given once in addition to oral prednisone at a dosage of 1 mg/kg.

A broad evaluation for bacterial and viral infection was performed including CSF PCR for herpes simplex virus-1 and -2, influenza, human herpesvirus (HHV) 6, varicella-zoster virus, Epstein-Barr virus and *Mycoplasma*. Influenza A and influenza B rapid antigen tests from nasopharyngeal swabs were negative, but two separate nasopharyngeal swab cultures grew influenza A. PCR studies from nasopharyngeal swabs were also positive for influenza A but were negative for influenza B and parainfluenza virus. The influenza A virus subtype was H1N1/New Caledonia, and the hemagglutination inhibition antibody titer for this subtype increased from <1/4 on Day 2 of the illness to 1/512 after 10 days. Antibodies to influenza A H3N2 and influenza B were detected at a lower level in early convalescent sera, presumably because of the patient's receipt of intravenous IgG on Hospital Day 9. The convalescent hemagglutination inhibition antibody titer to influenza A New Caledonia was 8-fold higher than to the other antigens, consistent with the virologically documented influenza A H1N1 infection. Table 2 lists the other infectious etiologies considered and worked up in this case.

Twelve weeks after the initial presentation, her

TABLE 1. Differential diagnosis for ANE and work-up in this case

Condition	Workup
Hypoxia	History, brain MRI
Toxins	Urine drug screen
Severe head injury	Head computerized tomography/brain MRI
Hemolytic-uremic syndrome	Complete blood count, renal function, urine analysis
Ischemic or hemorrhagic brain injury	Coagulation studies (PT, PTT, ATIII, protein C, protein S, Factor V mutation analysis, brain MRI, brain MRA, brain MRV
Meningitis/encephalitis*	Spinal tap, TUES*
Sepsis	Blood cultures
Metabolic derangement	Electrolytes, lactic acid, renal function
Inborn error in metabolism	Urine organic acids, homocysteine levels, plasma amino acid levels
Cardiac failure/endocarditis	Transthoracic echocardiogram, blood cultures
Seizure disorder	EEG
Acute disseminated encephalomyelitis	CSF, brain MRI, disease course
Reye's syndrome	Ammonia concentration, hepatic enzymes
Autosomal dominant ANE	History
Medium chain acyl-coenzyme A dehydrogenase deficiency	Acylcarnitine profile, glucose
Neurodegenerative disorders	History, brain MRI
Rheumatologic disorders	ESR, RF, anticardiolipin antibodies, ANCA, ANA, brain MRI

* The patient was enrolled in the Tennessee Unexplained Encephalitis Study (TUES).

PT, prothrombin time; PTT, partial thromboplastin time; ATIII, antithrombin III; MRA, magnetic resonance angiography; MRV, magnetic resonance venography; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; ANCA, anti-neutrophil cytoplasmic antibody; ANA, antinuclear antibody.

TABLE 2. Infectious etiology considered and worked up in this case*

Infectious Agent	Study
Influenza A virus*†	NP swab rapid antigen test, NP swab viral culture, NP swab PCR, CSF PCR, HAI serology, CSF viral culture
Influenza B virus*†	NP swab rapid antigen test, NP swab viral culture, NP swab PCR, CSF PCR, HAI serology, CSF viral culture
Parainfluenza virus 1–3*†	NP swab viral culture, NP swab PCR
RSV	NP swab rapid antigen test
HSV-1*	CSF PCR
HSV-2*	CSF PCR
HHV-6*†	CSF PCR
VZV*	CSF PCR
EBV*	CSF PCR, serology
CMV	Urine antigen and culture
Rotavirus*	Rectal swab rapid antigen test
HIV-1/HIV-2	Exposure history
Enterovirus*	Rectal swab viral culture
Rabies virus	Exposure history
Mycoplasma pneumoniae†*	CSF PCR, serology
Bartonella henselae (cat-scratch disease)	Exposure history

* Evaluation was part of Tennessee Unexplained Encephalitis Study.

† Reported association with ANE.

NP, nasopharyngeal; HAI, hemagglutination inhibition; RSV, respiratory syncytial virus; VZV, varicella-zoter virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus.

mental status returned to baseline, but ambulation remained difficult. She was able to walk but not to run because of compromised balance. A 2-month follow-up MRI demonstrated interval improvement in the previous involved regions and continued evolution of the thalami hemorrhages. At an 8-month follow-up MRI, continued decrease in size and enhancement of the bilateral thalamic lesions was noted. No new lesions were seen. Six months after the illness, the patient had returned to her previous level of cognitive functioning and was attending preschool. The only residual deficits were tremulousness with fine motor activities and mild strabismus.

DISCUSSION

Acute necrotizing encephalopathy, first described in 1995 by Mizuguchi et al.,[2] has been linked to influenza, as well as other infectious illnesses such as with HHV-6[4] measles,[5] parainfluenza virus[6] and *Mycoplasma*.[7] The hallmark of this type of encephalopathy is multifocal, symmetric brain lesions affecting the thalamus bilaterally, brainstem tegumentum, cerebral periventricular white matter and cerebellar medulla, which can be visualized best by MRI.[3, 8] Our patient had MRI findings consistent with those described in ANE, and influenza A virus was isolated from the upper respiratory tract; therefore this patient appears to be the first patient described in the United States with ANE related to documented influenza A infection. Charney et al.[9] reported an infant in 1979 with encephalitis and decreased density in the thalamic region, who might have been the first case of ANE in the US; however, MRI studies were not available, and there was no association with influenza virus. In 2001 Ravid et al.[10] and Bassuk et al.[11] reported a case of ANE in a 12-year-old girl and a 14-month-old girl, respectively, with characteristic MRI findings. In both cases no organism was identified. Sazgar et al.[12] recently re-

ported a case of influenza B ANE from Canada. In the past influenza A has been much more commonly associated with ANE than has influenza B.

The proposed diagnostic criteria for ANE include acute onset encephalopathy with convulsions, lack of CSF pleocytosis or increased blood ammonia, symmetric multifocal brain lesions and exclusion of resembling diseases, such as hypoxia, prolonged hypotension, hemolytic-uremic syndrome, severe head injury, intoxication, metabolic diseases or neurodegenerative disorders.[3, 12] The majority of published ANE cases occurred among previously healthy children <5 years of age. As with our patient the clinical course of ANE is remarkable for acute onset of mental status changes, most often within the first 24 to 48 h of influenza symptoms, accompanied by seizures. An increase in CSF protein of variable degree has been noted in many patients with ANE[2, 3], yet a CSF pleocytosis is usually not present.

In children with influenza-associated encephalopathy, influenza RNA was rarely detected, and the few autopsy studies done did not detect influenza antigens in brain tissue samples.[13] We were not able to identify influenza by PCR in the cerebrospinal fluid of our patient, although virus was detected in a nasopharyngeal swab with the same molecular assay. In influenza-associated encephalopathy reported in Japan, the possibilities of a dual infection with influenza virus and HHV-6, -7 or both or reactivation of latent HHV-6 or HHV-7 in the brain by influenza virus have been discussed.[4] In our patient we did not detect HHV-6 in the CSF by PCR.

The mortality of ANE reaches ~30%.[2, 3] Abnormal liver function tests and decreased platelets were the strongest predictive factors regarding mortality. A clinical presentation similar to that of ANE is seen in Reye's syndrome, but the characteristic elevation in serum ammonia and decrease in glucose are not present in patients with ANE. Encephalopathy, fatty liver and sudden death in children can also be a complication of medium chain acyl-coenzyme A dehydrogenase deficiency.[14] Our patient did not have hypoglycemia recorded at any time during her course, nor was an acylcarnitine profile obtained.

No specific therapy for influenza-associated encephalopathy is currently available. Supportive care, antiviral therapy, methylprednisolone pulse therapy and large doses of IgG reduced the mortality from influenza-associated encephalopathy from 30% to 15% in Japan (T Morishima, personal communication). Because cytokine-induced neurotoxicity is one possible cause of bad outcome, large dosage corticosteroid therapy may be beneficial.[15] Amantadine therapy for influenza encephalopathy has been tried in Japan with uncertain success.[16] Treatment of influenza B-associated encephalitis with oseltamivir resulting in CSF clearance has been described.[17] Because recent infection with influenza A was documented in our patient, treatment with amantadine and oseltamivir was given.

The pathogenesis of ANE is unknown but necropsy findings in fatal cases of ANE reveal diffuse cerebral edema and perivascular hemorrhage in the bilateral thalami and putamina.[3, 18] Congestion of arteries, veins and capillaries; acute swelling of oligodendrocytes; progressive rarefaction of tissue; and necrosis of neurons and glial cells are present suggesting a breakdown of the blood-brain barrier. The lack of significant infiltration of inflammatory cells in the CSF differentiates ANE from acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis. Many patients with these two diseases have a prolonged course, prominent focal signs and asymmetric or atypical distribution of brain lesions and predominately white matter involvement, features that are incompatible with ANE.

The cases of ANE concomitant with influenza infection reported from Japan provide a strong argument for a causal association, although the pathogenesis remains unclear. The rapidity of the onset of symptoms and the lack of viral antigen in brain tissue suggest that direct invasion of brain parenchyma and resulting cytopathic effect is not the mechanism but rather a cytokine-mediated process. Other factors that might be involved in development and/or progression of disease are a genetic predisposition in the Japanese or Asian population and the use of nonsteroidal inflammatory drugs used preferentially in Japan, such as diclofenac sodium, mephenamate, β_2-adrenergic agents and ephedrine.[19]

In summary we describe a pediatric patient who displayed the classical clinical features of ANE in association with a documented influenza A infection. Physicians taking care of children in the United States should be aware of this unusual but emerging presentation of influenza encephalopathy.

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Oral valganciclovir in children: single dose pharmacokinetics in a six-year-old girl

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We report a pharmacokinetic study in a 6-year-old girl with congenital human immunodeficiency virus type 1 and cytomegalovirus coinfection maintained on iv ganciclovir for 6 years. Increasing infection and thrombosis caused by her iv device necessitated alternative therapy. Single dose pharmacokinetics of ganciclovir 4.4 mg/kg iv and valganciclovir 13.2 and 26.3 mg/kg po were studied with high performance liquid chromatography/tandem mass spectrometry. The two oral dosages yielded areas under the concentration curve of 14.3 and 28.7 μg·h/ml, equivalent to 43% bioavailability of ganciclovir from valganciclovir, which exceeded the area under the concentration curve of 11.1 μg·h/ml yielded by ganciclovir 4.4 mg/kg iv. Oral valganciclovir achieved therapeutic and dosage-proportional plasma concentrations in the child we studied.

INTRODUCTION

Currently licensed anti-cytomegalovirus (CMV) agents include ganciclovir,[1] foscarnet[2] and cidovir.[3] Acute CMV infection in the immunocompromised host can be controlled by several such agents, including intravenous ganciclovir,[4] the drug of choice for CMV treatment in children. In the pre-highly active antiretroviral therapy era, AIDS patients required lifelong maintenance prophylaxis after successful induction therapy of opportunistic CMV disease. In adults this has been achieved with oral ganciclovir dosing. In children, however, there is no consensus dosing regimen for the 250-mg capsules, which deliver oral bioavailability of only 6 to 9%, with substantial interindividual differences in plasma values from similar doses.[5] Treatment involving 8-hourly dosing with ≥30 mg/kg becomes unrealistic because of the quantity of

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